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DATE: January 30, 2004

SUBJECT: COMMENTS ON THE DEPARTMENT OF PESTICIDES REGULATION'S S,S,S-TRIBUTYLPHOSPHOROTRITHIOATE (DEF) RISK CHARACTERIZATION AND EXPOSURE ASSESSMENT DRAFT DOCUMENTS

The Office of Environmental Health Hazard Assessment (OEHHA) has received and reviewed the Risk Characterization Document (RCD) and Exposure Assessment Document (EAD) prepared by the Department of Pesticide Regulation (DPR) for the active ingredient, S,S,S-tributyl phosphorotrithioate (DEF, tribufos). OEHHA reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and under the Food and Agricultural Code, Section 13129, in which OEHHA has authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

Currently, there are two products registered in California which contain DEF as the active ingredient, DEF 6 and Folex 6 EC. The products are used solely to defoliate/desiccate cotton in preparation for machine harvesting. Both products are formulated as emulsifiable liquid concentrates. DEF is considered by OEHHA, under Proposition 65, to be a chemical which may meet the criteria set forth in Title 22, California Code of Regulations, Section 12306 for listing as known to cause carcinogenicity (California Environmental Protection Agency OEHHA, September 29, 2000) and is listed as a Toxic Air Contaminant (TAC).

The documents submitted provide a broad overview of the available studies and scientific literature relevant to the toxicology of DEF. For the most part, OEHHA agrees with the presentation and discussion of the toxicology and risk assessment issues in these documents. Although the current versions of the documents are quite comprehensive, they could be improved by clarifying certain issues and expanding the information provided.

A summary of OEHHA's comments on the RCD and EAD for DEF is found below. For more details please refer to the attachment.

1. OEHHA suggests that the input of the new studies on the risk assessment be thoroughly discussed and that the differences between new and previous estimates be presented in a separate section of the document. The document would also benefit by discussing and comparing approaches used in DEF risk assessment by DPR and the United States Environmental Protection Agency (U.S. EPA).

2. OEHHA suggests that the Summary of Toxicology data and the labels of DEF products be included in the packet of DEF documentation submitted for review. OEHHA would like to know whether labeling information mentions cancer or TAC listing.

3. OEHHA supports the choices of critical studies and toxicological endpoints used in the DPR RCD for DEF.

4. In general, OEHHA supports DPR's evaluation of DEF oncogenicity and acknowledges the thorough weight of evidence analysis that includes discussion of the US EPA approach, genotoxicity studies and consideration of a structure-activity relationship.

5. OEHHA suggests discussing the apparent deficiencies of the mouse oncogenicity study.

6. OEHHA highly recommends including a discussion (under the "Weight of Evidence for Oncogenicity") of future approaches and possible methods and/or new studies that would help prove or disprove the current belief (notion) that DEF is a threshold-type carcinogen.

7. No information is provided within the RCD and EAD documents to show which oncogenic risk estimates are considered by DPR as acceptable and/or negligible from the health point of view. A clear statement on this issue would not only benefit the documents but would be helpful for health risk managers in their decisions on future actions to appropriately regulate the use of DEF in California.

8. OEHHA suggests that a brief summary of all uncertainties relevant to DEF risk assessment be included under the "Risk Characterization" section of the document. The current version of this section is limited to the description of the methods used for calculating non-oncogenic and oncogenic risk estimates.

9. No potentially sensitive subpopulations are discussed in the RCD other than children and infants. OEHHA recommends that a brief discussion of other potentially sensitive subpopulations (elderly, medical conditions) be added to the document.

10. The RCD is missing information on the potential hazard of DEF for nontarget terrestrial and aquatic animals. This type of information is usually provided for other pesticides under the "Environmental Fate" section of the RCD document.

11. OEHHA recommends including specific information regarding the existence (or lack) of current exposure benchmarks such as the reference dose, maximum contaminant level, threshold limit value, and permissible exposure limits etc. in the RCD.

Thank you for the opportunity to review the DPR documents. We hope that you will find our comments useful. Should you have any questions regarding this review of DPR's RCD and EAD, please contact Dr. Jolanta Bankowska at (510) 622-3162, Mr.Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

Attachment

ATTACHMENT

COMMENTS ON THE DEPARTMENT OF PESTICIDES REGULATION'S S,S,S-TRIBUTYLPHOSPHOROTRITHIOATE (DEF, TRIBUFOS) RISK CHARACTERIZATION DOCUMENT (RCD) AND EXPOSURE ASSESSMENT DOCUMENT (EAD)

COMMENTS

Documents submitted for review

The packet submitted for OEHHA review includes revised versions of the RCD and EAD prepared by DPR in June 19, 1997. The current version of the RCD has three appendices: appendix A (Equations for Inhalation Studies), B (Oncogenicity Computer Printout) and C (DEEM Acute and Chronic Dietary Analyses Printouts). The packet does not contain a useful document, Summary of Toxicology Data prepared by DPR Medical Toxicology Branch, which describes the current status of the data gaps. A hard copy of the RCD has numerous incomplete or missing pages (for example 7, 14, 16, 18, 53). It is not clear whether this was caused by a result of formatting or whether changes were made within the text but not in the Table of Contents. An example is the section "Acute Toxicity" listed in the Table of Contents under "Toxicology Profile" B, page 16. This part of the document is missing or might have been moved to another part of the document (pg. 79?).

OEHHA suggests that the Summary of Toxicology data be included as a part of documentation relevant to health risk assessment of pesticides and that the available data and discussions presented in the RCD for DEF be organized in a more coordinated manner.

DEF health risk assessments

The DEF health risk assessment under review was initiated because new data were submitted by the registrant. The new data included three neurotoxicity studies in rats (acute, subchronic and developmental) and a dermal absorption study in monkeys. The new data changed the outcome of the risk assessment. Overall, the new risk estimates show that exposure to DEF results in less risk than previously determined. The greatest change was caused by the dermal toxicity study in monkeys, which decreased dermal exposure estimates to about one seventh of the former estimates.

OEHHA suggests that the input of the new studies on the risk assessment be thoroughly discussed and the differences between new and previous estimates be presented in a separate section of the document. The document should also discuss and compare approaches used in the DEF risk assessment by DPR and the US EPA (June 26, 2000).

Selection of critical studies and endpoints for risk assessment in RCD

OEHHA supports the choices of critical studies and toxicological endpoints used in the DPR RCD for DEF.

Groups sensitive to DEF exposures

No potentially sensitive group of the human population other than children and infants is mentioned or discussed in the document. OEHHA recommends including a discussion of other potentially sensitive subpopulations (elderly, medical conditions) in the RCD.

Potential oncogenic effects

Oncogenic effects caused by DEF were produced only in one species, mice (Hayes, 1989). The study showed a significant increase in adenocarcinomas of the small intestine in both sexes, liver hemangiosarcomas in males, and alveolar/bronchiolar adenomas in females. Not only was there an increase in tumors in multiple sites, but a significant increase of adenocarcinomas of the small intestine in both sexes is of special importance, because this is a rare type of tumor in the mice tested (CD-1). The study lasted 90 weeks and the doses tested were: 0,10, 50 and 250 ppm in a diet. Equivalent doses in male mice were 0, 1.64, 8.28, or 48.02 mg/kg/day and 0, 2.08, 11, 14 or 63.4 mg/kg/day in female mice.

U.S. EPA has classified DEF as an "unlikely human carcinogen" because all tumor increases occurred only at the highest dose tested (48.02 mg/kg/day in males and 63.4 mg/kg/day in females) and was accompanied by severe toxicity. The Health Effects Division (HED) Cancer Peer Review Committee (CPRC) concluded that the overall evidence indicated that DEF is a "likely human carcinogen" at high doses, based on increases in tumors in both sexes of CD-1 mouse, in the liver of male mice, in the lung of female mice, and in the small intestine in both sexes of mice. The CPRC recommended a non-quantitative approach (i.e., non-linear, Margin of Exposure) for the purpose of risk characterization using the most sensitive toxicological endpoint. The CPRC did not recommend a low-dose linear approach (i.e., q_1^*) because of severe accompanying toxicity, common for organophosphate chemicals, which occurred at all doses in the mouse. DEF is considered by OEHHA, under Proposition 65, to be a chemical which may meet the criteria set forth in 22 CCR Section 12306 for listing as known to cause carcinogenicity (CAL/EPA OEHHA, September 29, 2000) and it is listed as a Toxic Air Contaminant (TAC).

DPR recognized and agreed with the CPRC assessment of the carcinogenic potential of DEF, but still performed its quantitative carcinogenic risk assessment. OEHHA supports DPR's evaluation and acknowledges the thorough weight of evidence analysis that includes discussion of the US EPA approach, genotoxicity studies and consideration of a structure-activity relationship. OEHHA acknowledges and supports inclusion of the quantitative carcinogenic risk assessment as a part of the overall health risk assessment of DEF.

In spite of severe toxicity observed in the mouse oncogenicity study, no apparent concerns for mutagenicity (negative mutagenicity tests) and no carcinogens known structurally related to DEF, a final conclusion about DEF oncogenic potential can not be made. Strong, positive results from the mouse study cannot be discounted. OEHHA suggests further discussion of the apparent deficiencies of the subject mouse study to address issues such as length of the study (90 not 96 weeks) and dose spacing (the mid-dose of 50 ppm is equivalent of 1/5 of the high dose of 250 ppm instead of the usually used ½ of the high-dose). A more appropriately designed study could have resulted in significant increases of tumors not only at the highest dose level tested but also at lower doses. Discussion (under the "Weight of Evidence for Oncogenicity") of future approaches and possible methods and/or new studies that would help prove or disprove the current belief that DEF is a threshold-type carcinogen is highly recommended.

DEF risk assessment uncertainties

Uncertainties involved in risk assessments in general and some uncertainties specific for DEF are mentioned in appropriate different parts of the documents. OEHHA suggests that a brief summary of all uncertainties relevant to DEF risk assessment be included under the "Risk Characterization" section of the document. This section could also address but not be limited to: the current status of DEF risk assessment, possible future requirements of new data that would allow further refinements of the risks, possible underestimations of the current DEF risk assessment on the risk of exposures to DEF (due to the lack of data on DEF metabolites and their contribution to DEF toxicity, lack of the methods to measure the impact of cumulative toxicity of DEF and other organophosphates and methods to measure the impact of the potentiation of toxicity between DEF and other organophosphates). The current version of the "Risk Characterization" section is limited to the description of the methods used for calculating non-oncogenic and oncogenic risk estimates.

Health risk results and potential regulations

The risk for non-oncogenic health effects in humans is expressed as a margin of exposure (MOE). As a general rule, a margin of exposure greater than 100 is considered protective of human health when it is calculated from a No-Observed-Effect Level derived from an animal study. The MOEs for acute neurological effects with occupational exposure ranged from approximately 55 for irrigators and weeders with a four-day Restricted Entry Interval to 2,000

for ground applicators. The seasonal MOEs were less than 100 for most pesticide workers (10 to 75), except ground applicators and module builder operators, who had estimates of MOEs higher than 100. The MOEs for acute dietary, combined acute dietary and ambient air and chronic dietary exposure to DEF in the various population subgroups are all considered acceptable from the health point of view.

The estimated oncogenic risk from occupational exposure to DEF was approximately 10^{-5} for most pesticide workers, except for ground applicators whose oncogenic risk was approximately 10^{-6}. The estimated oncogenic risk from dietary exposure and combined dietary and ambient air exposure was between 10^{-6} and 10^{-7}. There is no information provided within the RCD and EAD documents as to which oncogenic risk estimates are considered by DPR to be acceptable and/or negligible from the health point of view. A clear statement on this issue would not only benefit the documents but would be helpful for health risk managers in their decisions on future actions to appropriately regulate use of DEF in California.

Label precautions

According to the EAD for DEF both DEF products DEF 6 and Folex EC bear the signal word Danger reflecting toxicity category I. The precautionary statements on both labels inform users of ingestion and inhalation hazards. The labels also warn users of possible eye and skin injuries. The labels of the DEF products were not included in the packet of DEF documentation submitted for our review. OEHHA would like to know whether labeling information mentions cancer or TAC listing.

Environmental hazard

The RCD does not contain information on the potential hazard of DEF for nontarget terrestrial and aquatic animals. This type of information is usually provided for other pesticides under the "Environmental Fate" section of the document.

Exposure standards

The RCD would benefit by providing information on the existence or lack of current exposure standards such as reference dose, maximum contaminant level, threshold value, and permissible exposure limits etc.

References

California Environmental Protection Agency Office of Environmental Health Hazard Assessment Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)

(September 29, 2000). Chemicals under Consideration for Possible Listing via the Authoritative Bodies Mechanisms: Request for Relevant Information.